May 13, 1951.

Dear Tom: Nelson

Thanks for all the news of Caltech. If it took a while for me to answer, it is because I've had a staff of cryptographers working on your message, and their report only just came in.

The affaire Rowley reminds me of an indident which took place in Ryan's lab, involving one of your pals with initials Arhold Ravin. Is there any connection between pro-Hinshelwoodism and his choice of problem? Do you know about the stuff Plough reported on the penicillin sensitivity of cysteineless Salmonella?

For the genealogy of s^+, most of the Y- strains are derived directly from 679-680, and therefore probably carry the same mutation. Do you want our current K-12? I also have the 58- and 679- whence the divergences may well have started.

The Lac- of Y-53 is Lac_1-. Its segregation behavior is described in my 1947 Genetics paper.

That application of streptomycin to tie down the zygote would be fine if it worked. Unfortunately, in e.g. 58-161 x W-1177, the proportion of S^r from isolations on non-sm medium is about 10%, and there is very little loss of the predicted yield if one first mixes the parents directly on sm medium. Streptomycin is evidently not as bactericidal as I had thought, and you can check this yourself by diluting and plating from cell-sm mixtures from time to time. You can do SRP (S^r-prototroph selection, as K-12 x W-1177) quite well in the same way. It should be possible to do the same thing much better using phage: this should be very easy for the Caltech group. With the stocks you already have, T1 or T5 would be applicable; otherwise throw in V_6^r in one parent.

That is, most of the expected S come through.

Dominance of s^+ in heterozygotes doesn't sound especially exciting, but if it has the right linkage relationships, it would be no trick to do. If it is linked to Mal (of 1177) or S^r, forget it, but if it is linked to Lac or Xyl or V_1, it would be no problem. There is a bit of an art to handling these diploids. If you really want to play with it, why don't you spend a week here sometime this summer and pick up the background. If you have the linkage data beforehand, and the stocks prepared, it shouldn't take much longer than that to settle it.

I'm not sure that I understand your project involving UV, but on generak grounds, I think it would be highly desirable to study the effects of UV in an unprejudiced way on recombination (including a checkup on the Texans). But I doubt whether the bactericidal effects of UV are at all simple. First of all, there's the Lwoff effect (and most K-12 stocks, including all of yours, are lysogenic). Secondly, diploid and haploid stocks show identical killing curves (and I don't think this is essentially because of overshadowing by the lwoff effect. Finally, very few lethals if any have turned up in our experiments on irradiating diploids, so that I doubt if this has much importance in killing. Finally (again), UV does cause some rather complex nuclear reorganisations whose influence in your expts. would be quite unpredictable.

For a few tidbits of our own: one of the new students here (Phyllis Fried) is cutting her teeth on the problem of complementary segregants, along the lines of Gordon Allen's expts. in MGB. She plates M-P- x T-L- on mt and pl agar, and eventually throws away everything but M-T- and P-L- recombinants. There are many other markers segregating (the T-L- is W-1177), and one would expect that these nutritionally complementary isolates would have statistically complementary distributions of the markers. Lac and V_1 are OK, but Mal is completely out: like the prototrophs, both of these classes are about 90% Mal-. Xyl and Mtl are intermediate. This is exactly as one would predict from the behavior of heterozygotes: in this cross Mal+ is usually eliminated, and the frequency of Mal+ is not determined by linkage to nutritional factors at all, but by the frequencies with which Mal+ as against Mal- is the segment which is eliminated. This in turn may be due to crossing over (to the centromere?) with the critical point from which the segmental elimination occurs. No effort yet to duplicate Allen's more difficult experiment, trying to get M-T- and P-L- out of the same zygote, but at least we won't expect Mal, S, etc. to be complementary among them.

The following is to be mentioned only in whispers until we're sure of our ground. Zinder finds recombination in Salmonella typhimurium, but Davis' "Bacterial Bundling Board" experiment which helps to exclude a filtrable intermediate in K-12, shows the converse here. It is probably not a transforming factor, for a great many different genes are carried together. The best bet is that the factor is like the filtrable L-form granules, which under our conditions will not germinate in ordinary broth, but will do so if growing cells of coli or Salmonella are present. But a preferance for gametic function rather than simple vegetative growth is iddicated. There will be more on this at CSH. If there really are filtrable, dormant, resistant forms of nonsporing bacteria, it is easy to see what happens to most of the "transformations". If they have gametic functions, then transformation may be a special case of sex instead of vice versa. It all depends on the true size and organization of the transforming agent, and I would certainly like to know more about this in the pneumococcus case.

Sincerely,

Joshua Lederberg